

**REMARKS**

In view of the remarks presented herein, the applicants request withdrawal of the rejections and favorable reconsideration of the claims.

**I. Status of the Claims**

Claims 1-2, 4-5, 7-19 and 21-38 are pending in the instant application. Claims 12-19 were previously withdrawn as being directed to non-elected species and claims 1-2, 4-5, 7-11 and 21-38 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over a variety of references. Applicants respectfully traverse the rejections.

**II. Rejection under 35 U.S.C. §103(a) should be withdrawn**

Claims 1, 2, 4-5, 7-11 and 21-38 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable under 35 U.S.C. §103(a) over Fricker (*Toxic. In vitro* 8(4): 879-881, 1991) combined with General & Applied Toxicology, (Vol. 1 Stockton Press New York, 1993 pages 11-20), in view of Eisenbrandt et al., (*Fd. Chem. Toxic.* 32(7): 655-669 1994) and Renwick et al. (*Regulatory Toxicol. and Pharm.* 18: 463-480, 1993) and further in view of previously cited Yao et al., Chung et al., Garza-Ocanas et al., and Morrison et al.

The Examiner cites Fricker as a primary reference and states that this reference "discusses the role of *in vitro* cytotoxicity testing in the selection and development of pharmaceuticals. In the introduction, the reference states that potential new products must first be assessed for performance but toxicity becomes important where such toxicity may place limitation on the products usefulness. The reference teaches that cytotoxicity testing is an effective way of further ranking the potential products and provides a simple method for selecting candidates for further investigation. The paper concludes that cytotoxicity testing can be used to rank similar chemicals or materials where knowledge of relative toxicity is required and as such can be incorporated into the selection procedure of a product research and development program." The General & Applied Toxicology paper ("GAT paper") is cited to show the importance of dose response analyses and as teaching that dosage of a given chemical to be tested can be used to detect the no observable effect level (NOEL). The Examiner further

combines Fricker and the GAT paper with Eisenbrandt et al. and Renwick et al., which are cited as teaching that the NOEL dose is a known parameter for the most sensitive toxicological effect. It is true that each of these references in some way addresses the area of a need for testing toxicity of a chemical compound. However, applicants respectfully traverse the construction that the Examiner has given to individual references, the existence of any motivation to combine the references, and the allegation that this combination of references renders the claimed invention obvious.

The references cited by the Examiner in general discuss the value of determining safe levels of a compound that is to be further used or developed for use in humans. However, none of these documents provide a teaching of the use of multiple *in vitro* assays to predict an *in vivo* toxicity level and using that multiple set of *in vitro* assays to select a NOEL value for predicting *in vivo* toxicity.

Fricker reviews four examples of *in vitro* testing used in industrial research and development programs. However, none of these examples meets the limitations of the presently claimed invention. For example, Fricker discusses a "tumour cell line panel" for examining the structure-activity interactions in a number of compound classes. From the discussion at page 879-880 it is evident that the "differential cytotoxicity" of the agent being tested is in a panel of different cancer cell-types and not a panel of different cellular health assays within the same cell-type as in the present claims. Moreover, in this context, Fricker uses "cytotoxicity" to refer to antitumor activity. (See p. 879, last full paragraph.) The discussion of "Biocompatible materials" at page 880 of Fricker merely recites two separate assays (cell viability and antibacterial activity) but again it was on two different cell types (i.e., cell viability on Vero cells (which are Green Monkey kidney cells) and antibacterial activity on *S. aureus* cells). Importantly, the bacterial assay was an activity assay, to test a compound for desired antimicrobial activity. Thus, no more than one of the assays pertained to prediction of cytotoxicity in a mammalian cell line. The metal ion antibacterial agents (described at 880 of Fricker) were tested against a number of different bacterial strains for activity and in CHO cells for cytotoxicity. Again, there is no mention of the use of at least three separate assays to test cytotoxicity of the agent within a single cell line and determine the NOEL in at least all three separate assays to determine the cumulative NOEL over all of these assays. Thus, while the

suggestion in Fricker is that the skilled artisan should employ certain cytotoxicity testing to rank the relative toxicity of similar chemicals (p. 880), there is no teaching in Fricker that such ranking should be performed in the manner suggested in the claim 1 of the present application.

The secondary references cited by the Examiner fail to remedy Fricker's deficiencies. The GAT excerpt paper is simply a teaching of how to prepare and analyze dose-response curves. It adds nothing to Fricker with respect to identifying a Ctox value in the manner described in the present invention. In fact, the GAT excerpt pertains to analyzing toxicity data obtained *in vivo* and teaches nothing about effective procedures for using *in vitro* data to predict toxicity *in vivo*.

Likewise, Eisenbrandt also pertains to *in vivo* toxicity testing. [See, e.g., Abstract ("studies that use a variety of species"); p. 655, column 1 ("the ultimate objective of animal toxicity studies"); p. 658, column 1 ("Test species age, time course and exposure pattern are important considerations"); p. 658, column 2 ("standard studies...are conducted...with different duration and routes of administration as well as with several species of animal"); p. 660, column 2 ("Behavioral tests"); etc.] In fact, Eisenbrandt's only significant discussion of "non-mammalian *in vivo* and *in vitro* methods" is a short paragraph on page 663, where Eisenbrandt says no *in vitro* test is widely accepted as a routine screening test for neurotoxicity and that such tests are appropriate only in exceptional cases. (See p. 663, column 1, first full paragraph.) Clearly, Eisenbrandt is not relevant to the claimed invention. Eisenbrandt is simply a review of various *in vivo* tests that are used for neurotoxicity studies. Eisenbrandt's discussion of multiple *in vivo* tests for assessing toxicity in no way discloses or suggests how to predict *in vivo* toxicity from *in vitro* tests.

Renwick, too, pertains to *in vivo* evaluations of toxicity, and is irrelevant to the present invention. This is captured succinctly in Renwick's introduction, which states that "The NOEL is usually derived from experiments in which groups of animals are given a range of doses of the compound...." (p. 403, emphasis added.) Thus, while Renwick uses the term "NOEL," Renwick does not use "NOEL" in the context of the claimed invention. Moreover, there is no teaching of a combination of assays all of which are used to produce a cumulative NOEL from at least three separate indicators of cell health.

The Yao *et al.*, Chung *et al.*, Garza-Ocanas *et al.*, and Morrison *et al.* which the Examiner cites only for the purposes of multiple concentrations and various different assays. The discussion from the response dated January 12, 2004 relating to these references is incorporated herein by reference.

As the foregoing discussion of each individual reference indicates, the Examiner has failed to cite a single or combination of references that suggest identifying a NOEL concentration as the highest concentration of a chemical compound at which a measurable toxic effect of the chemical is not observable in at least three cell-based assays; predicting *in vivo* toxicity based on a NOEL selected this way; determining a TC<sub>50</sub> for each of the indicators of cell health ( required element of claim 4); a method of identifying a lead compound for drug development (claim 31) or numerous other features of the other dependent claims.

Moreover, no where in the rejection has the Examiner articulated a reasonable basis for combining any two or more of the references. A suggestion to combine references is a prerequisite for any obviousness rejection based on multiple references.

Furthermore, the articulation of the rejection at pages 5-6 of the office action fails to provide a comparison of the teachings of references to the claims or evaluation of differences between them, which are also required steps for an obviousness analysis. Instead, the Examiner has pointed to generalities about "the prior art documents taken as a whole" and the alleged conventionality of individual elements (cytotoxicity tests) and individual terms (C<sub>tox</sub>, ETI, NOEL). In so doing, the Examiner has failed to appreciate that cited references use terms (e.g., NOEL) in a manner different than the claims, and the Examiner has failed to identify a combination of references that suggest combining all of the elements of claim 1 (or other claims) into a single method for predicting *in vivo* toxicity.

For all of these reasons, the Examiner has failed to establish that any of the claims are rendered obvious by cited combination and Applicants request that the rejection be withdrawn.

### III. Concluding Remarks

Applicants submit that each of the presently pending claims in this application is

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believed to be in condition for allowance. Please address all future correspondence to Pfizer,  
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